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(54) Moulding quick-dissolving dosage units

(57) Solid shaped articles containing a predetermined quantity of chemical, such as pharmaceutical dosage units which are capable of being rapidly disintegrated in water, are prepared by freezing a composition containing partially hydrolysed gelatin in a mould and then subliming solvent from the frozen composition. The composition is frozen by means of a gaseous cooling medium.

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SPECIFICATION

Solid shaped articles

This invention relates to a process for preparing a solid shaped article carrying a predetermined unit quantity of a chemical. In particular the invention relates to a process for preparing such an article which is capable of being disintegrated by water at 20°C within 5 seconds. Examples of such articles are described in U.K. Specification 1548022.

According to the invention there is provided a process for preparing a solid shaped article carrying a predetermined unit quantity of a chemical, the article being capable of being disintegrated by water at 20°C within 5 seconds, which process comprises filling a composition comprising the predetermined amount of chemical and a solution of partially hydrolysed gelatin into a mould, freezing the composition in the mould by passing gaseous cooling medium over the mould and then subliming solvent from the frozen composition so as to produce a network of partially hydrolysed gelatin carrying the chemical.

The products of the process are useful for many different applications, particularly where it is desired to administer, dispense or otherwise utilise a chemical in predetermined unit quantities. For example, certain chemicals which are used in solution or suspension form but which are difficult or hazardous to transport or store in such form may be converted by the process of the invention into a solid form which can be added by the user to an aqueous medium to produce the desired solution or dispersion containing a predetermined amount of the chemical. Further, the chemical may be a chemical reagent such that the product of the process of the invention may be added to a known amount of aqueous liquid to produce a standardised liquid composition which can be used, for example, in chemical analysis. Further, the chemical may be a diagnostic compound which it is desired to add to a biological sample (e.g. blood, urine) in order to determine the amount of a particular constituent present in the sample. However preferably the chemical is a pharmaceutical substance and the solid shaped article carrying the predetermined unit quantity of pharmaceutical substance is a pharmaceutical dosage form.

Pharmaceutical dosage forms produced by the process of the present invention are particularly suitable for oral administration. When orally administered the pharmaceutical dosage forms generally disintegrate rapidly in the mouth (e.g. within one or two seconds) and thus the dosage form is a particularly advantageous means for administering pharmaceuticals to humans, and also to non-human animals. The dosage form produced by the process of the invention can be used as an alternative to a tablet, pill or capsule, particularly in patients who have difficulty in swallowing conventional dosage forms.

The first step in the process of the invention is the step of filling the composition into the mould. The mould can be, for example a depression in a metal plate (e.g. an aluminium plate). The plate may contain more than one depression, each depression being of the size and shape corresponding to the desired size of the shaped article. However the mould is preferably a depression in a sheet of filmic material. The filmic material may contain more than one depression. The filmic material may be similar to that employed in conventional blister packs which are used for packaging oral contraceptive tablets and like medicament forms. For example the filmic material may be made of thermoplastic material with the depressions formed by thermoforming. The preferred filmic material is a polyvinyl chloride film. Laminates of filmic material may also be used.

The partially hydrolysed gelatin may be prepared by heating a solution of gelatin in water, e.g. in an autoclave at about 120°C for up to 2 hours, e.g. for about 30 minutes. The hydrolysed gelatin is preferably used at concentrations of about 1 to 6% w/v, most preferably at 2 to 4%, e.g. about 3%.

Besides the chemical and the hydrolysed gelatin, the composition may contain other additional ingredients. For example, when preparing pharmaceutical dosage forms the composition may include pharmaceutically acceptable adjuvants such as colouring agents, flavouring agents, preservatives and the like. In addition the composition may contain ingredients which aid in the preparation of the shaped articles. For example, the composition may include a surfactant, e.g. Tween 80 [polyoxyethylene (20) sorbitan mono-oleate], to aid in the dispersion of the chemical. The composition may also include ingredients such as fillers (e.g. mannitol, sorbitol) which improve the physical properties of the shaped article.

The solvent for the composition is preferably water but it may contain a co-solvent (such as an alcohol) if it is desired to improve the solubility of the chemical.

The desired quantities (e.g. 0.3 ml to 1.0 ml) of the composition may be filled into the moulds using, for example, an automatic filling machine.

The composition in the mould is frozen by passing gaseous cooling medium over the mould. The gaseous cooling medium may be passed over a stationary mould or the mould may be moved through the gaseous cooling medium source or, preferably, both the mould and the gaseous cooling medium may be moved. For example in a preferred embodiment, the mould containing the composition is conveyed through a chamber in one direction and gaseous cooling medium is drawn or forced through the chamber in the opposite direction. For example liquid nitrogen may be injected into the chamber. The liquid nitrogen vapourises and the gaseous nitrogen is then drawn through the chamber by fans as a counter current to the moving mould. By controlling the rate of injection of the liquid nitrogen, the speed of the fans and the speed of

the conveyance of the mould the freezing rate may be accurately controlled. The liquid nitrogen could be replaced by other liquefied gases (e.g. liquid argon or fluorinated hydrocarbons).

When the composition has been frozen the solvent may be sublimed from it. If desired, the frozen compositions may be stored in a cold store before the sublimation process is carried out. The sublimation may be carried out in a freeze drier by subjecting the frozen composition in the mould to reduced pressure and, if desired, controlled application of heat to aid the sublimation. The pressure can be below about 4 mm Hg, e.g. below 0.3 mm Hg, for example 0.1 to 0.2 mm or even below 0.05 mm Hg. The initial temperature in the freeze drier may be, for example, as high as 60°C and this temperature can be reduced (e.g. to 50°C) as the temperature of the frozen composition increases.

After the sublimation process the shaped articles may be removed from metal moulds and stored for future use. If, as preferred, the mould is one of a number of depressions in a sheet of filmic material a covering sheet may be adhered to the filmic material so as to produce a package enclosing the shaped articles. The covering sheet is preferably an aluminium foil or aluminium foil laminate which may be adhered to the filmic material around the depressions by, for example, a heat sensitive adhesive. The covering sheet is preferably adhered to the filmic material such that it may be peeled away from the filmic material by the user so as to expose the dosage forms in their depressions.

The sublimation step results in the production of a shaped article comprising a network of the partially hydrolysed gelatin, the network carrying the chemical. The network which is similar in structure to a solid foam enables a liquid to enter the product through the interstices and permeate through the interior. Permeation by aqueous media exposes both the interior and the exterior of the shaped article to the action of the aqueous media whereby the network is rapidly disintegrated. The disintegration time of the product can be determined to see whether it is capable of being disintegrated by water at 20°C within 5 seconds using a standard tablet disintegration apparatus as described in British Pharmacopoeia, 1980, Vol II, Appendix XII A but with the standard 2.00 mm wire mesh replaced by stainless steel 40 mesh screen. A sample product is placed in a dry tube held above the surface of the water. The apparatus is started and the sample immersed in water at 20°C. The sample should disperse on the liquid surface and any solid residue should pass through the 40 mesh screen within 5 seconds.

The following Example illustrates the invention

EXAMPLE 1

Pharmaceutical Dosage Forms containing 30 mg oxazepam

Formulation:

Oxazepam		30	mg
Tween 80 BPC		0.375	mg
Mannitol BP		22.5	mg
3% hydrolysed gelatin	to	0.75	ml

The 3% hydrolysed gelatin is prepared by suspending 30 g of powdered gelatin in 800 ml of cold distilled water in a 1 litre flask and autoclaving it at 121°C for 60 minutes. When cool, the final volume is adjusted to 1 litre.

Oxazepam (40 g) is suspended in 3% hydrolysed gelatin solution containing dissolved mannitol (30 g) and Tween 80 (0.5 g) using ultrasonics for 5 minutes and the suspension made up to 1 litre with 3% gelatin solution. 0.75 ml portions of the suspension are dosed, using an automatic filling machine, into pockets in polyvinyl chloride blister trays. The trays are then placed on a conveyor which passes along a tunnel. Liquid nitrogen is injected at the other end of the tunnel. The liquid nitrogen vapourises and fans in the tunnel blow the gaseous nitrogen cooling medium as a counter current to the trays moving on the conveyor. The rate of injection of the liquid nitrogen, the speed of the fans and the speed of the conveyor are adjusted so that the composition in the blister is frozen as the trays pass through the tunnel.

The blister trays containing the frozen compositions are transferred to a freeze drier. The pressure is adjusted to 0.5 mm Hg. The temperature of the shelves in the freeze drier is set at 60°C for 1½ hours and then lowered to 40°C. After 6 hours the trays are removed from the freeze drier. A peelable aluminium foil is then sealed to the blister pack around the depressions containing the pharmaceutical dosage forms. The pharmaceutical dosage forms disintegrate rapidly, for example, in two seconds or less, when taken orally. When tested by the procedure described hereinabove they are disintegrated by water at 20°C within 5 seconds.

EXAMPLES 2 to 11

Following the procedure of Example 1, similar pharmaceutical dosage forms are prepared containing the following active ingredients:—

Example

2 Oxazepam 15 mg and 50 mg

3 Lorazepam 1, 2, 2.5 and 4 mg

4 Temazepam 10 and 20 mg

5 Lormetazepam 1 mg

6 Frusemide 40 mg

7 Bendrofluazide 5 mg

8 Cyclopenthiazide 0.5 mg

9 Isosorbide dinitrate 2.5, 5 and 10 mg

10 Indomethacin 25 and 50 mg

11 Prochlorperazine maleate 50 mg

CLAIMS

1. A process for preparing a solid shaped article carrying a predetermined unit quantity of a chemical, the article being capable of being disintegrated by water at 20°C within 5 seconds, which process comprises filling a composition comprising the predetermined amount of chemical and a solution of partially hydrolysed gelatin into a mould, freezing the composition in the mould by passing gaseous cooling medium over the mould and then subliming solvent from the frozen composition so as to produce a network of partially hydrolysed gelatin carrying the chemical.

2. A process as claimed in Claim 1 in which the gaseous cooling medium is gaseous nitrogen.

3. A process as claimed in Claim 1 or 2 in which the composition is frozen by conveying the mould containing the composition through a chamber in one direction and passing the gaseous cooling medium through the chamber in the opposite direction.

4. A process as claimed in any one of the preceding claims in which the solid shaped article is a pharmaceutical dosage form and the chemical is a pharmaceutical substance.

5. A process as claimed in any one of the preceding claims in which the mould is a depression in a sheet of filmic material.

6. A process as claimed in Claim 5 in which a covering sheet is adhered to the filmic material around the depression or depressions containing the solid shaped articles.

7. A process for preparing a solid shaped article substantially as hereinbefore described with reference to any one of the Examples.

8. A solid shaped article whenever prepared by the process of any one of the preceding claims.

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